**REMARKS**

Claims 1-8, 11, 14, 15, 37 and 54-59 presently appear in this case. No claims have been allowed. The official action of June 25, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to hydrophilic inclusion complexes that are nano-sized particles of a water insoluble lipophilic compound surrounded and entrapped within an amphiphilic polymer. The inclusion complex renders the lipophilic compound soluble in water. The invention further relates to a method for forming such an inclusion complex by adding a low concentration solution of the lipophilic compound in a non-aqueous solvent to a turbulent zone in an aqueous solution of the amphiphilic polymer. The aqueous solution is heated to a temperature above the boiling point of the non-aqueous solvent. By this procedure, the hydrophilic inclusion complex is formed.

The interview among Examiners Lewis and McCain, and the undersigned attorney, who was accompanied by the inventor, Dr. Rina Goldshtein and another representative of the assignee, Dr. Irene Jaffe, conducted on November 30, 2004, is hereby gratefully acknowledged. In this interview, a brief PowerPoint presentation was given explaining the nature of the

invention. Proposed new claims were discussed in order to even better distinguish over the prior art, and the references of the rejections were discussed. The examiner also provided applicants with a new prior art reference, Janes et al "Chitosan nanoparticles as delivery systems for doxorubicin" *J Control Release* 73:255-267 (June 15, 2001). Applicants explained that this reference did not anticipate. The reference is directed to the entrapment of a hydrophilic molecule into nanoparticles formed by ionic gelation of the positively charged polysaccharide chitosan (see the second sentence of the abstract). Thus, a major difference is that the active molecule of the reference must be hydrophilic, while in the present claims the active molecule must be lipophilic. In view of this difference, the other differences in the structure of the nanoparticles need not be discussed.

In the course of the interview, Dr. Lewis questioned the difference between "encapsulation" and "complexation". Applicant's representatives pointed out that microencapsulation produces a structure which is not an inclusion complex of a water-insoluble lipophilic compound surrounded by and entrapped within an amphiphilic polymer. The polymer will be cross-linked to completely surround that which is encapsulated. Because of this difference, there will be differences in chemical and biological stability

properties. Applicant's representatives further pointed out that, regardless of the difference in properties, to the extent that there is no anticipation, the claimed inclusion complexes would not be obvious from a reference to microencapsulated nanoparticles, because one of ordinary skill in the art would not know how to go from one to the other. It is only by means of the novel process of the present invention that the novel hydrophilic inclusion complexes can be formed.

A Request for Continued Examination (RCE) was filed in this case on September 27, 2004, accompanied by an amendment and response to the June 25, 2004, Office action. Thus, the present invention is in the nature of a supplemental amendment intended to supplement applicant's amendment of September 27, 2004. It is respectfully requested that this supplemental response be admitted pursuant to 37 C.F.R. §1.111(a)(2), which became effective on October 21, 2004. The undersigned attorneys were appointed to this case on October 21, 2004, and thus it was not possible to review the claims and file a supplemental amendment prior to the effective date of the new rule. Accordingly, it is urged that the examiner exercise his discretionary authority to enter this supplemental amendment, assuming that it reaches the examiner in sufficient time to be entered into the application file before the examiner considers the prior amendment. In the

explanatory notes accompanying the rule-making package of September 21, 2004, the following statement appears at 69 FR 56517 (2004):

> Examiners may enter and consider other supplemental amendments that are not listed in section 1.111(a)(2)(i).

From this, it is clear that the examiner has the discretion to enter this amendment. Accordingly, this amendment should be entered because of the special situation that applicants were unaware that the rule would be changed with respect to supplemental amendments at the time that they were considering switching attorneys, and it would therefore be unfair to apply the new rule to the present supplemental amendment in the present case.

Furthermore, the present supplemental amendment should be entered in accordance with 37 C.F.R. §1.111(a)(2)(i)(C) or (F), as it is believed that the present amendment will place the case into condition for allowance. At the very least, it will obviate at least one of the rejections, thus simplifying issues for appeal. Accordingly, acceptance and entry of the present supplemental amendment prior to issuance of the next official action is respectfully urged.

In the official action of June 25, 2004, claims 1-7 and 50 were rejected under 35 U.S.C. §102(b) as being

anticipated by Liversidge. This rejection was discussed in the amendment accompanying the filing of the RCE, and claim 1 was amended at that time. These arguments are fully applicable and are adopted herein. They were discussed in some detail in the course of the interview. Liversidge does not describe an inclusion complex as is required by the claims. Furthermore, the particles of Liversidge must be crystalline, while the particles of the present invention are deposited from a molecular solution and do not have time to form any crystalline structure. In Liversidge, the surface modifier is merely adsorbed on the surface of the crystalline drug. This is not structurally identical to a lipophilic compound that is surrounded by and entrapped within an amphiphilic polymer. Accordingly, Liversidge cannot anticipate the present claims. Furthermore, the present invention cannot be made obvious by Liversidge as there are no secondary references that would suggest the obviousness of any modifications that would be necessary in order to change the crystalline particles of Liversidge, with adsorbed surface modifier, into an inclusion complex. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 8-18, 33-49 and 51-53 were rejected under 35 U.S.C. §103(a) as unpatentable over Rolfes in combination with Parikh and Liversidge.

The present supplemental amendment clarifies significant differences between the process of the present invention and that of Rolfes. Claim 8 requires that the lipophilic compound be in a low concentration solution, which is added to a turbulent zone in an aqueous solution of the polymer heated to a temperature above the boiling point of the non-aqueous solvent. Only by mixing low concentration lipophilic material in a non-aqueous solvent into a turbulent zone of the aqueous solution carrying the polymer, which aqueous solution is at a temperature higher than the boiling point of the non-aqueous solvent, is it possible for the solvent to flash off at the same time that the amphiphilic polymer wraps around the lipophilic compound that was carried in the solvent, so as to form an inclusion complex which is essentially soluble in water. None of the references of record disclose the criticality of such temperature differences in the use of a turbulent zone. Accordingly, claim 8, particularly as presently amended, clearly defines over the references of record. Reconsideration and withdrawal of this rejection is also respectfully urged.

The claims as provided to the examiner in the interview have been amended slightly in order to delete "and bioavailable" from claim 8, and to add that in a dependent claim. This was done for the same reason that it was done for

claim 1 and new dependent claim 55 was added, as discussed at the interview. Not every possible utility for the inclusion complex of the present invention is pharmaceutical. Cosmetic uses, for example, may not require bioavailability. Accordingly, it is not necessary for this statement to be in the independent claims. It is now being added in dependent claims.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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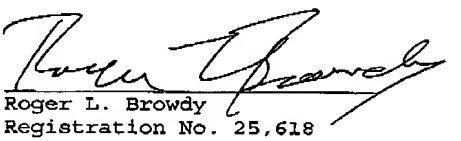
By 
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this **SUPPLEMENTAL AMENDMENT** is being facsimile transmitted to the Patent and Trademark Office, on the date shown below.

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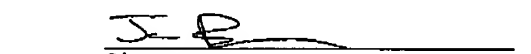
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